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Regulating Shapes and Sizes

Mutations at many loci lead to altered shapes and sizes, suggesting complex regulation of the overall morphology of an organism. Two recent studies present data on how orientation of growth axes and perception of maturation signals might regulate growth processes.

About 75 years ago J.B.S. Haldane suggested that there was a most "convenient" size for every animal and that higher animals (and plants) were not larger because they were more complicated, but, rather, more complicated because they were larger. The sizes and shapes of organisms and organs within them are generally faithfully conserved within a species, suggesting a genetic control over these parameters. What regulates shapes and sizes of organisms or organs is a fundamental question that has continually intrigued developmental biologists. Over the past decades, a hypothesis has emerged that organisms measure and monitor size to maintain the normal size. In animals, generally, changes in cell size can be compensated for by changes in cell number to maintain a final size (Day and Lawrence, 2000). In contrast, plants can attain larger overall size if cell size is increased by polyploidization and demonstrate overall size compensation only in mosaic organs (Harberd and Freeling, 1989). Alterations in cell division planes (leading to abnormal cell arrangement) or in *CDC2* function (leading to fewer cells) do not alter overall size or shape (Hemerly et al., 1995). However, plant organs are sensitive to perturbation in size in only one axis and can show either narrower or shorter leaves if cells fail to elongate in the length or width dimension (Tsuge et al., 1996). The missing link between a gene product, which is responsible for the final structure, and the actual elaboration of final form remained unelucidated.

A recent study on genetic control of the surface curvature of leaves in *Antirrhinum* attempts to fill in some of the gaps in our knowledge about the regulation of form (Nath et al., 2003). Several genes are known to be involved in the development of flattened outgrowths like wings and leaves. Mutants in these genes often show curvature defects (Waites and Hudson, 1995). The mechanical control exerted by these genes over the nature of the outgrowth had not been described. Nath and coworkers report on a TCP transcription factor, *CINCINNATA* (*CIN*), which affects leaf curvature dramatically. In wild-type *Antirrhinum*, leaves are flat and elliptical, whereas, in the *cin* mutant plants, leaves are crinkly and round. In *cin* mutant leaves, crinkliness is caused by extra growth due to prolonged cell divisions. Wild-type *Antirrhinum* leaves mature in a wave moving from the tip to the base. In the *cin* mutant, cells in the proximal and distal regions resemble those in wild-type leaves in maturation rates. However, analysis of *HISTON4* and *CYCLIN D3b*, markers for the cell division, showed that maturation is delayed and the cells divide for a prolonged period of time in the middle region of *cin* leaves. These extra cell divisions due to the delayed maturation in the middle region of *cin* leaves generate the negative curvature, leading to a crinkly leaf. *CIN* mRNA accumulates to higher levels in leaf margins compared with the medial region and correlates with the expression of *H4* and *CYCLIN D3b*. The authors concluded that *CIN* acts to make the marginal cells more sensitive to perception of maturation signal and allows termination of cell proliferation in a timely manner.

In a related study, Rolland-Lagan and coworkers were able to demonstrate growth dynamics during petal development in *Antirrhinum* by utilizing a new system combining classical clonal analysis and growth modeling (Rolland-Lagan et al., 2003). While clonal analysis has been a useful tool for studying the lineage of a certain group of cells or structures, this method has a limitation. It is difficult to interpret the direction of growth based on the final clonal sectors. The authors compared clones sequentially throughout petal development and combined these clonal data with growth parameters. Wild-type *Antirrhinum* petals are asymmetric. Surprisingly, this petal asymmetry is created because of directional growth perpendicular to the main axis. This is true for both the adaxial and abaxial sides of the petal. Scanning electron micrographs (SEMs) showing axialized cell shapes coinciding with the direction of growth predicted by the model confirmed the validity of this modeling method. The authors also examined whether asymmetry in petal shape is due to differential growth rates. They found that differential growth rates at certain times in development are not crucial for final petal shape because averaged growth rates over time and space also generate the same petal shape. Instead, the final petal shape is determined by anisotropy (growth occurring in a preferred direction). The authors suggest that long-range signals orient the growth direction in the petal as a whole because this directional growth is maintained throughout the petal development.

These two papers quantify and describe the sequence of events leading from perturbations at the level of the gene product to the growth events that elaborate a final shape and size. This new modeling system developed by Rolland-Lagan and coworkers will allow exploration of how cell divisions and cell expansions are controlled to generate certain developmental structures and how known genes are involved in these processes. Many mutations lead to altered shapes and sizes of organs, suggesting that several genes have a role in regulating shape and size. Rolland-Lagan and coworkers provide an accessible tool for comparing the growth patterns in these mutants with the wild-type. This will allow one to assess how these genes affect the rate, location, or direction of cell divisions and elongation at a certain developmental stage. It seems to be generally true that alterations in either cell proliferation or cell size alone do not affect final organ shape and size, suggesting possible mechanisms that sense the final dimension and regulate it by altering the other parameter (Hemerly et

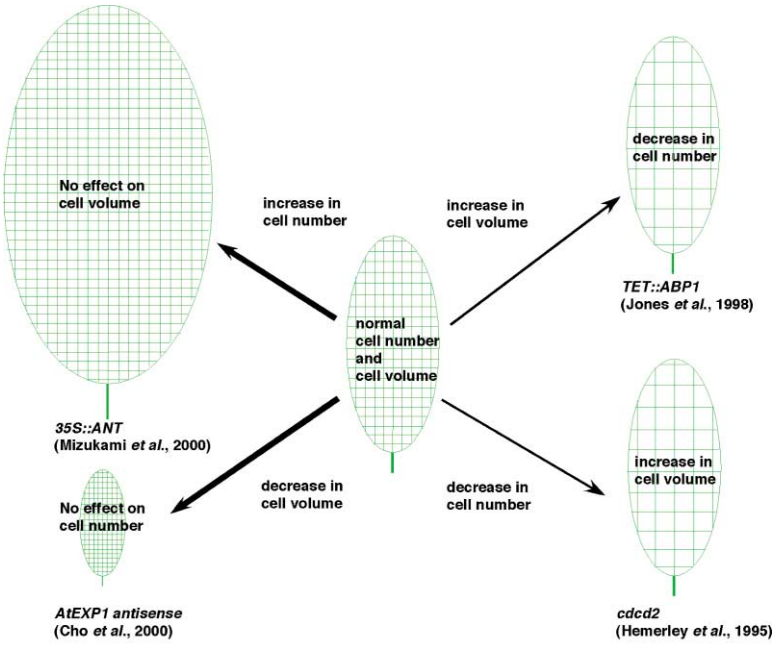

Figure 1. The Regulatory Relationship between Cell Number and Cell Volume

Leaves can compensate for increases in cell volumes by decreasing cell numbers and for decreases in cell numbers by increasing cell volumes. However, increased cell numbers are not compensated for, nor are decreases in cell volume. This suggests that compensation mechanisms that favor increased cell size are possible, while those that prevent this (by altering processes regulating cell size) or increased cell numbers are not possible in plants (or have yet to be discovered).

al., 1995; Jones et al., 1998). However, several examples suggest that compensation of increased cell proliferation by reduction of cell size or decreased proliferation by increasing cell sizes might not be always true (Figure 1; Cho and Cosgrove Daniel, 2000; Mizukami and Fischer Robert, 2000). Timing may be a critical "third dimension" that determines whether compensatory mechanisms will come into play or not. In addition to timing, these mechanisms are likely governed by multiple other components. These components need to be discovered in years ahead.

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Selected Reading

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All Roads Lead to ATF4

Multiple intracellular stress pathways converge on a single event—phosphorylation of the translation initiation factor eIF2α and subsequent translational activation of the transcription factor ATF4. Exploring the consequences of this event has highlighted the ways in which stress is sensed and responded to via many distinct pathways.

Cellular mechanisms for sensing and responding to stress underlie the ability of cells to withstand the many insults, both programmed and exogenous, that are encountered during development and differentiation. It is becoming increasingly evident that common pathways are shared in the responses to multiple, seemingly divergent stresses, yet the logic for this common response has been unclear. Now, a paper by Harding and colleagues (2003) in the March issue of *Molecular Cell* illustrates how the activation of one transcription factor by multiple stress pathways forms the basis of a generalized stress response.